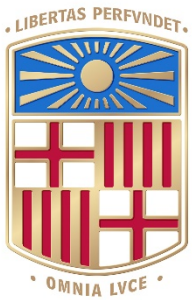


UNIVERSITAT DE BARCELONA

Final Degree Project

**Biomedical Engineering Degree**

# "Conceptualization and ideation of a wearable device to predict HE"

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## Abstract

Hepatic encephalopathy (HE) is a pathology believed to be produced when the liver function is impaired and cannot adequately remove toxins from the blood, such as ammonia, which leads to a buildup of toxins in the bloodstream that can reach the brain and affect its function. Some patients that present cirrhosis may be eligible to have a TIPS (*Transjugular Intrahepatic Portosystemic Shunt*) implanted, which decreases the pressure in the portal vein and improves their liver condition. However, clinical evidences have shown that HE is more likely to appear in patients that have had a TIPS implanted. This work is a first stage of a project that aims to create a device able to predict the development of HE on patients that have an implanted TIPS and also study the causes of this pathology. Since ammonium is the only proven biomarker for HE, an initial study was performed to discuss which other ions or molecules could have a correlation with the development of HE. Additionally, since there is a correlation between the ammonium concentration in blood and sweat, a non-invasive sensor that measures the ammonium concentration in sweat was conceptualized and designed. Because this device is non-invasive, could be worn in daily life and it allows a simple maintenance that does not require a technician, it would present an advantage over the current diagnostic techniques since they are invasive or mainly based on psychological tests.

## Acknowledgments

First of all, I would like to thank my director, Dr. Anna Baiges, who proposed the project, invited me to their leading-edge unit where I was able to observe a TIPS implantation and that has answered very fast and efficiently all my questions regarding the clinical issues of this project. Also, I would like to thank my tutor, Mario Garcia, for accepting to be my tutor and encouraging me to investigate further this field and to develop this project.

Moreover, I would like to thank Dr. Jordi Colomer from the Biomedical Engineering department for his inestimable help and knowledge regarding the sensor conceptualization.

I would like to personally thank my mom, who has read my whole work and listened patiently to my non-ending new ideas, although this is not her area of expertise, and has put my mind at ease many times during the writing process. Additionally, I would like to thank my closest friends that have lifted me up each time I thought that I was not going to finish this project, which happened more times I want to admit.

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# 1. Introduction

## 1.1. Objectives

The first objective is to study and consider different screening methods that can be used to diagnose hepatic encephalopathy (HE) in advance, taking into account its wide range of symptoms. The second objective consists in choosing and discussing which of the studied methods should be used and to demonstrate their feasibility and logistics.

Therefore, this project would aim to solve the current need of monitoring the possible symptoms of patients who are sent home after TIPS surgery in order to detect early the onset of hepatic encephalopathy and send them to the hospital for treatment, thus avoiding possible casual accidents that may be caused by disorientation. The ideal goal would be to detect as many symptoms and obtain as many data available as possible in order to use machine learning algorithms that could predict such disorder several hours before it can become dangerous for the patient.

Moreover, since hepatic encephalopathy has not been studied thoroughly and there are no clear proven biomarkers used to detect the disorder, being diagnosed mainly by using psychological tests and by considering the liver problems of the patient and the procedures performed on him, an additional task consisted on proposing other parameters that could be added, using similar methods, to the presented project that could be found useful to detect the mentioned disorder.

To sum up, the following list exemplifies the main objectives and milestones of this project:

- A study of the current diagnostic tools used to detect hepatic encephalopathy on patients that have an implanted TIPS.
- An analysis on the necessity of a device able to predict hepatic encephalopathy for patients that have undergone the TIPS procedure.
- A comparative study of the different solutions presented to monitor the patient's possible symptoms.
- A study based on clinical correlation with different ions that would be useful to diagnose or predict HE before an episode occurs.
- The conceptualization of a biosensor able to monitor continuously the concentration of ammonium present in the patient's sweat.

### 1.2. Methodology and location

Originally, this project was proposed by Dr. Ana Baiges and Dr. García-Pagan who work on the Hepatic Hemodynamic team in Hospital Clinic. In order to develop this project, we had a few meetings with the group, where they introduced the clinical part of the project and explained with plenty of detail how the HE pathology works, how it is currently diagnosed and treated and the symptoms that are used to confirm the presence of this pathology. Moreover, they provide us some ideas of solutions that had been devised to detect some of the clinical parameters.

An important part of this project was a rigorous study of this pathology and the ideation of different methods or techniques that we could use to monitor the biological parameters of this patient from home and a thorough study on some other biological parameters that could be add in this project in order to find out if they have a clinical correlation with HE and, thus, be used as biomarkers for this concrete pathology.

Once the project was defined and the different possibilities were studied, a clinical immersion was performed where the Hepatic Hemodynamic unit of Hospital Clínic was visited. There, we had the opportunity observe a TIPS implantation procedure in person and understand how the surgery was performed and each step followed, which included the measurement of the portal vein pressure and the introduction of the catheter, the stent implantation that takes around 2-3 hours and the final pressure measurement and further possible dilatations needed.

Additionally, during our visit, we proposed to the team the ideas we had for the project and discussed which was the best approach and which ions or substances were most clinically relevant. Moreover, we also discussed with the medical experts the logistics of the project regarding the patients' conditions after the procedures, their stay in the hospital and their recovery process being able to also observe the rooms reserved for the post operatory patients and the installations of the whole department. We also had the opportunity to contact with specialists that perform the minimal hepatic encephalopathy tests weekly and observe the instruments used in the test and some of the results obtained from the previous years.

Furthermore, after deciding that this project would be focused on the detection of clinically relevant ions present in sweat and studying which ions provide more relevant information on HE, the biosensor that would be used to perform the measurements was designed and conceptualized. This conceptualization of the biosensor was done with the help of one professor from the

Biomedical Engineering department of the physics' faculty and its components and modules are explained in great detail.

### 1.3. Scope and span

In this section the most relevant limitations present in this project will be discussed. Generally, since it is a final degree project, there are a wide range of limitations that concern both time and resources. Moreover, extra limitations are included since these projects are based on a clinical field and, thus, extra regulations when designing or implementing the project practically will be applied.

Another limitation consisted on the lack of papers or bibliography regarding both the HE, which has very unclear analytical diagnostic parameters, and the sweat sensor since it just gained relevance as a medical product a few years ago due to technology improvements. Therefore, making the proposals of this project very hypothetical. Moreover, since it is a very new field of technology, there were not many experts on this field available to be consulted.

In addition, since this is a six-months project it would be nearly impossible to design from the very beginning a prototype of a device that integrates all the diagnostic tools nor get the approval for the clinical trials and experimentally test it on a wide number of patients to perform a data analysis that will allow to diagnose this pathology earlier, which is exactly what the whole proposed project entails. Therefore, this project represents a first stage for this device conceptualization, focusing on the possible study of sweat detected ions that could have a clinical correlation with the development of HE.

## 2. State of the art

For a better comprehension of the work done, an initial review of the hemodynamic hepatology field will be exposed. It has been taken into consideration the main aspects involved in this final degree project, which are the implantation of a Transjugular Intrahepatic Portosystemic Shunt (TIPS), that can lead to the development of a hepatic encephalopathy as well as the current diagnostic tools used.

### 2.1. Hepatic encephalopathy description.

The main purpose of a functional liver is to regulate chemical levels in the bloodstream and secrete bile which helps to carry away the waste products from the liver. Substances coming from the stomach and intestines, that are absorbed into the bloodstream, pass through the liver where they are processed and toxins are removed. Many of these toxins, such as ammonia, are usually breakdown products obtained through the digestion of proteins.

Hepatic encephalopathy (HE) is believed to be produced when the liver function is impaired and cannot adequately remove the toxins from the blood. This leads to a buildup of toxins in the bloodstream that can reach the brain and affect its function. It is thought that this pathology is due to the passage of ammonium into the general bloodstream and accumulation in the brain in the form of different substances that alter its functions.

This pathology is usually classified using the West-Haven criteria, which differentiates four different grades of clinically manifest HE. In grade I, patients only show lack of attention and subtle personality changes that are recognized mainly by their relatives. In grade II, the patient experiments disorientation combined with inappropriate behavior and lethargy. In grade III, patients are stuporous but are yet able to respond to stimuli, are very disoriented regarding place and situation and also behave bizarrely. Grade IV is given to patients that have already entered a coma. However, when it was discovered that patients may show alterations of brain function in neuropsychological or neurophysiological measures without displaying signs of HE, a fifth grade was added and called minimal HE [1].

Finally, we can differentiate between two different main types of encephalopathy which are the sporadic one and the triggered one. While in the first one the causing factors have not been yet standardized, clinical evidences show that the development of sporadic HE is more likely to appear in patients that have had a TIPS implanted. However, it is thought that some triggering factors for

the spontaneous HE could be infections, gastrointestinal bleeding, diuretics and electrolytic disturbances. The triggered encephalopathy is hypothesized to be caused by several factors such as electrolytic disturbances, infections, constipation, fever and the intake of certain medications among others.

### 2.2. TIPS procedure and consequences.

In patients that present cirrhosis, a late stage of scarring and inflammation of the liver, the liver impedes the circulation at the portal vein increasing its pressure and promoting further complications of the disease. For these patients a TIPS, which consists of creating an intrahepatic connection between the portal vein and the systemic circulation avoiding the obstruction and reducing the hypertension, is usually performed. When a TIPS is placed, the blood stream coming from the gut containing the toxins that would be removed in the liver, bypasses the liver cells and, therefore, is not detoxified. When this blood flow containing toxins reach the brain, promotes the development of HE and, hence, patients that require a TIPS have a higher risk of developing HE.

The implementation of a TIPS is a minimally invasive procedure consisting of inserting a stent in the channel between the portal and hepatic veins to keep them open using a balloon-tipped catheter. As well as being less invasive than traditional bypass surgery, this procedure carries fewer risks. However, although it can help reduce the risk of further liver complications, it cannot correct existing liver damage.

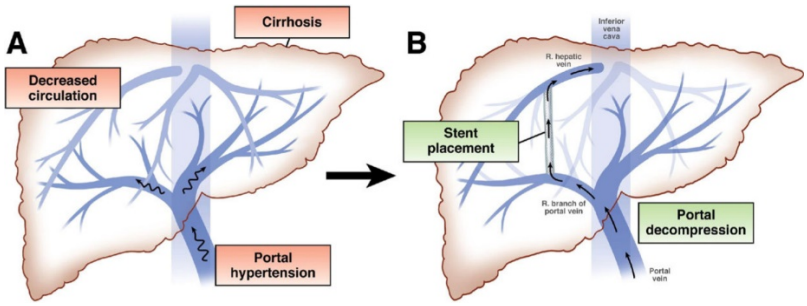


***Figure 1.*** Cirrhotic liver anatomy with TIPS implementation drawing.

The purpose of this procedure is to decrease the portal pressure since the risk for hemorrhage decreases as well. However, the more this pressure is decreased, the higher is the risk of suffering an HE episode. Therefore, nowadays the pressure that was initially at 25 mm Hg and was always dropped below 12, is now considered to be enough to drop it at 13 – 14 mm Hg. It has been proven that the procedure is more efficient if there is an equilibrium between the amplification of the vein

radius, and thus the portal pressure, and the consideration of the side effects, that will include the HE.

There are two types of patients that are treated, the controlled patients that are usually admitted to the hospital the night previous to the procedure and the ones that have an emergency procedure. After the procedure is performed, the patients will stay until the next day at the hospital where their vital signs will be monitored, they will be checked for bleeding and their portal pressure will be checked again. It is important to check the portal pressure the next day since during the procedure, when the final portal pressure is checked, as the patient is under the effects of anesthesia and using mechanic ventilation, the pressure values could be altered. The next day, this pressure will be checked using a catheter and it will not require anesthesia. Generally, if the patient does not show any signs of complications and the portal pressure is inside an approved range, the patient will be discharged and allowed to go home.

Regarding the risks that this procedure entails, while people that have portal hypertension may benefit from the TIPS procedure, this surgery can lead to additional complications, one of them being the hepatic encephalopathy. According to a study on long-term effects of transjugular intrahepatic portosystemic shunt on cirrhotic livers performed in 2017 involving 98 people with portal hypertension, 36.7% of the participants developed hepatic encephalopathy after undergoing this procedure [2].

Therefore, although most individuals have a relatively low risk of developing complications after a TIPS procedure, they still require monitoring during the recovery process in order to ensure that the side-effects are minimum.

### 2.3. Current HE diagnostic techniques.

Initial HE symptoms include sleepiness, flapping (shaky hands) or other movement problems, changes in mood and personality, disorientation, and jumbled and slurred speech among others. As these symptoms appear to be psychological, doctors perform mental status tests looking for the subtle changes that occur in the early stages of HE.

There are also physiological parameters that can be assessed such as ammonia levels, which are found to be abnormally high in 90% of the cases, or increased heart rate and temperature which may occur before or heralding the HE development. However, ammonia is a negative predictive

value since it only indicates an abnormality in the liver or kidney and, hence, high blood ammonia levels alone do not add any diagnostic.

Currently, the techniques used in order to diagnose this pathology consist of a combination of neurological and clinical tests. The neurological tests are usually used in patients that present a minimum hepatic encephalopathy and are now being performed before the TIPS procedure is done in order to study if there is a real correlation between the TIPS procedure and the risk of suffering from HE or if this pathology is already present before the procedure is performed and, thus, it is only a cause of the cirrhosis. There are three main neurological tests used to diagnose the minimum HE, which are the FEIX, FLICKER and animal test since the neurological tests are affective but time-consuming and a universal 'gold standard' test has yet to be agreed upon.

The FEIX test consists on ordering numbers or letters on a paper and comparing the time that these patients take to perform the test to a standardized time for healthy patients using the RedEH platform. The animal test is aimed for the illiterate patients and consists on naming as many animals as possible for a minute. Finally, the FLICKER is a test that consists on putting on some sort of augmented virtual glasses that show a small red spot and a big white circle. The test measures the frequency at which the patient perceives that the red-light spot becomes a flickering light while the device causes a stepwise decrease in frequency. This test is performed multiple times and then the average time taken to perceive it and the standard deviation are computed and compared to the standard patient.

The clinical tests consist on measuring corporal temperature, heart rate and blood levels of ammonia. Moreover, some dynamic symptoms can be easily observed on the patients such as shaky hands, jumbled speech and disorientation although some of these symptoms might indicate that a move advanced HE. In addition, since patients that have a TIPS have an increased probability of suffering an episode of HE due to its liver malfunction, it is easier to diagnose them with this pathology. However, although currently there are not any monitoring devices used to diagnose or predict an HE episode, there are some sensors that can be applied in the mentioned case that are being used in other medical fields.

## 3. Market research.

In the early stages of HE development, there are a few dynamic symptoms that can be measured using already in the market medical technology. From the aforementioned symptoms, the easiest to detect using on-the-market medical sensors are ammonia levels, heart rate, temperature, flapping (shaky hands) and slurred speech.

Therefore, although this project is focused on the sweat analysis in order to detect different ions that will later be discussed, this section includes the search of other diagnostic tools that are already in the market or that have been developed as investigation projects for other pathologies, that can be also used for the prediction and detection of HE.

First of all, we will explain the evolution of the market and its drivers around the field of wearable devices used to perform different non-invasive tests that will allow the obtention of data from different parameters depending on the need. In addition, we will also focus on the ion-detection devices, used to measure ion concentration in body fluids such as sweat.

### 3.1. Market evolution, drivers and barriers.

Focusing on wearable sensors, we cannot deny that the need for trustable data regarding the body status of a patient or potential patient, has caused a rapid increase in the reported projects or papers published about this field over the last ten years. This experienced growth in the field of wearable medical sensors is undoubtedly connected to increasing market expectations that predict that, for instance, electronic skin patches will reach $ 10bn by 2023 as immediate revenue, though these numbers are based mainly on the success of physical sensors over chemical ones.

The medical wearables market is segmented into devices used for diagnostic or monitoring, therapeutic devices, rehabilitation devices and devices used for health and fitness. Mainly, wearable sensors currently on the market are used for health and fitness tracking by measuring parameters such as dehydration, muscle activity and exercise intensity [3].

A number of current trends occurring in healthcare are driving the use of wearables. From the patient's point of view, that would be the growing proportion of elderly population, the growing popularity on technology use for almost everything, an increased popularity for health and wellness and a trend towards personalized preventative care. From the physician side, the increasing demand of these devices comes from focusing on "big data" analysis that interpret large amounts of collected data combined with analytical tools such as AI and ML, the improvement of

technologies such as the miniaturization of the sensor technologies and the trend of treating patients making an emphasis on preventive and personalized care.

However, just as certain trends are driving the healthcare wearable market forward, there are certain market factors that these wearables currently encounter after being designed, that are inhibiting its market. Again, from the patient side, they would be the high cost of wearables and concerns over privacy issues. From de physician side of view, some are less likely to encourage their use due to a perception of poor quality of data and a lack of clinical evidence supporting them [4]. Moreover, regulations regarding medical devices are extent and thorough and, hence, slow down the pace of innovation in this field.

### 3.2. Monitoring of sweat ions' concentrations.

Using sweat for disease diagnostic is not new, since for decades cystic fibrosis in newborns has been screened testing their sweat. However, the process of collecting and transporting the biofluid was more complicated than an ordinary blood test and, therefore, the technology did not catch on.

However, since there has been a major improvement in microfluidics and electronics and researchers have discovered that perspiration may present more information being easy to stimulate, collected and analyzed than originally though, in the last five years there has been an urge to develop sensors able to measure sweat parameters.

#### *3.2.2. Wearable sweat sensors.*

Lately, there have appeared on the market skin patches, which are thin, soft, adhesive patches containing electronic systems that are stuck onto skin. They can use a battery to power or not to power themselves and be reusable or disposable. The aim of this devices is to provide information about the patient's blood pH, sweat rate, and blood chemistry including levels of chloride, glucose and lactate among others. These devices allow faster diagnosis using electrolytes or other chemistry abnormalities that signal early signs of diseases, enable the track of the treatment progress and allow the doctors to monitor the patients' recovery remotely, intervening in case of necessity.

However, for skin patches to reach a wider consumer base, there are several technical challenges that first must be overcome such as adhesive degradation, materials and design, data type and interpretation and patient's behavior. Given more time for validation, clinical recognition, regulations

along with improvements in the manufacturing processes, skin sweat patches are expected to be key in remote patient monitoring in many medical disciplines [4].

There is a noticeable trend towards measuring ions in sweat due to the high ion content that the substance has (on the range of mM), the simplicity of the sample and the easy adaptation of daily objects, such as sweatbands and patches, to use them to be in contact with the skin for the measurements. However, in order to collect the sweat sample, a sufficient amount of sweat is needed and, while it is very compatible when the sensor is applied to physical activity, in the medical field it is necessary to expose the patient under some circumstances in order to increase their sweat rate [5].

*3.2.2.1. Wearable potentiometric sensors*

Wearable potentiometric sensors are currently receiving much attention due to their great potential involving ion detection in sweat. In spite of the significant progress regarding the potentiometric sensors being integrated in wearable devices, there is plenty of room for improvement in terms of materials, manufacturing processes and strategy for sample collection. Mainly, these sensors are currently used during sport performance and the majority of papers written on the subject from the last five years describe the on-body tests while the individual wearing the device is practicing an activity. The utilization of these devices on the medical field is very limited and almost only studied in the context of cystic fibrosis diagnostic. [5]

*3.2.3. Monitoring of sweat ammonium levels.*

Blood ammonia levels are currently determined in a laboratory using a blood sample. This method to measure the levels of ammonia is considered invasive as it requires taking a blood sample. However, recent studies have shown that there is a relation between the blood and sweat ammonia levels and, therefore, this physiological parameter can be measured using wearable devices that are currently being validated in sports sciences [6]. Moreover, sweat sensing presents the advantage of being a continuously accessible biofluid which makes it an ideal candidate for prolonged semicontinuous ammonia monitoring. Furthermore, sweat sensors can be simply placed on the skin near a sweat-generation site and perform fast measurement [7].

A fully integrated wearable sensor consists on two main components, which are the sweat collector and the sensor. Although most wearable sweat-sensing devices are intended for athletes, currently, in the market, there are also sweat-collection mechanisms aimed to collect very small amounts of

sweat ideally for sedentary patients. As for the sensing part, currently the only way to measure the $NH_4$ analyte in sweat is using the potentiometry technique, which measures the potential between a sensing electrode and a reference electrode which are in contact with the sweat sample [7].

### 3.3. Other symptoms monitorization.

Since the initial proposed project was to create a device that integrated as many diagnostic tools as possible to detect all the currently known symptoms, the following section was added, which shows the market and situation of other techniques and devices that could be used to detect other physical symptoms.

#### *3.3.1. Heart rate monitorization using wearable devices.*

Heart rate monitorization might be the easiest dynamic symptom to measure due to the availability of wearable devices that integrate the heart rate monitorization. Currently in the market there are different devices such as waistbands, wristbands or armbands that are used as activity trackers that monitor heart rate and easily transmit the data to a mobile phone using Bluetooth. The most common types of pulse trackers are chest straps and optical heart-rate monitors. Usually the more accurate ones are the chest straps, which contains electrodes that are located against the chest skin that measure the electrical activity of the heart, however, as they require sweat to pick up the electrical signal, this is ideally designed to be applied in sport sciences. The optical monitors use the reflection of light onto the flowing blood through the skin in order to measure blood flow [8].

The probability of having HE at a certain moment is high when the patient has an increased heart rate, hence, the accuracy of the heart rate is not essential but whether the heart rate is or not in an abnormal rate range is. Therefore, conventional wearable devices using photoplethysmography to measure heart rate would be acceptable for this case. Moreover, several of these devices include the ability of also monitoring temperature, which is another relevant parameter to evaluate for the HE prediction.

#### *3.3.2. Hand tremors recordings and analysis.*

Essential tremor research in Parkinson's disease that has been developed these recent years consisted in the use of inertial sensors, accelerometers and gyroscopes in order to detect physical involuntary movements. Sensors are placed usually in the upper extremities using a wristband and using machine learning (ML) algorithms they can objectively distinguish the hand tremors [9] [10].

As flapping, which consists on having shaky hands, looks similar to the resting tremor, this technology can be applied in our case to detect the aforementioned symptom.

*3.3.3. Detecting slurred speech.*

Slurred speech, which is known as dysarthria in the medical field, is characterized by poor pronunciation of the words or a slower rhythm during talking. In the last year, there are several computer science researchers that have studied the possibility of detecting dysarthria from a simple sentence-level audio recording using ML algorithms. These studies are based on the fact that speakers suffering from dysarthria tend to have irregular rhythmic patterns, which they try to detect in order to diagnose dysarthria [11] [12].

# 4. Regulations and legal aspects

Considering that this project is focused on the design of a project that uses several medical devices (for direct biochemical measurements and biological signals) in order to diagnose in advance an HE, it is necessary to follow the very strict regulations imposed in the medical market and make sure all the technical requirements for commercializing the product are fulfilled.

In our case, the project involves several different medical devices and each one of them has different standards and regulations that must be achieved in order to obtain the CE stamp for the European Union. Moreover, nowadays legislation in the biomedical engineering field does not only cover the medical device hardware part but also regulates the software part. The concerning legislation for this project has been divided in different sections in order to efficiently expose the different laws.

## 4.1. Medical devices

This first section will consider the general legislation regarding the commercialization of any medical devices for both the device measuring the heart rate and temperature, and the sensing-patches used for sweat ion-detection. It will take into account both the hardware of the devices and the implemented software that would be used.

### *4.1.1. Hardware*

First of all, since it is a medical device, it needs to guarantee general quality, safety and efficiency features of the device and its manufacturing process. Moreover, it must have a reliability superior to that required for domestic equipment. These requirements are included in the ISO 13485, which specifies the standards that are universally accepted and basically consist of quality management systems for medical devices.

The aforementioned ISO is specific for the medical field and is an extension of the widely known ISO 9000. These regulations entail a detailed list of medical devices classes, definitions and conditions of quality management systems for both the final product and the production process.

Concretely, since the device should be in contact with the skin, it is required to guarantee the safety standards mentioned in ISO 10993, which describes the procedure for the assessment of medical devices and their constituent materials regarding their potential to produce irritation and skin sensitization [13].

*4.1.2. Software*

According to the definition of a medical device posed by the Medical Devices Directive 2007/47/EC, some of the software used in the medicine field is already considered to be a type of medical device under the current legal framework. It is specified that it is the intended purpose of the software which determines whether if it should be in deed considered a medical device or, on the contrary, even when used in healthcare settings, to not be consider it.

The MDD defines medical device software as any software intended by the manufacturer to be used for human beings for a medical purpose such as diagnosis, prevention, monitoring, treatment or alleviation of the disease. The project proposed is included in the diagnosis section, so it is clearly considered to be a medical device software. [14]

The MDR has updated the rules determining the risk classification of medical devices specifically addressing software. It has stated that software that acts on the decision-making of a determinant diagnostic or therapy can range from Class IIa to Class III depending on the impact that will have this decision over the patient, which could be irreversible deterioration of health of a patient or death. In order to get the CE marking, all medical device manufacturers that produce Class II or Class III devices, which is the case of this device since it is a diagnostic tool, must be approved by a Notified Body (NB). [15].

Moreover, for point of care devices that are aimed to be used at home and transmit the gathered information to a external computer system so the doctor is able to track the patient's progress, must stand by ISO/IEEE 11073 Health informatics - Medical that regulates the communication between medical, health care and wellness devices and with external computer systems. [16]

**4.2. Data protection**

Contrary to other physic devices in the medical field, the laws regarding a software developed to make a diagnostic from chemical analytes data obtained also involve the security in the treatment of medical data of the patient. The privacy of the patients, the integrity of the medical data and the posterior availability of the biomedical data obtained, for authorized personnel, must be ensured. As the data used in the project consists of human medical data, its use is subjected to specific regulations on both European Union and national level which controls the distribution of human data and the use of it in research.

In Spain, and concretely in Catalonia the main laws to be considered in order to transfer and use personal health information for research are the following ones:

- Organic Law 15/1999 on the Protection of Personal Data
- Catalan law, Llei 21/2000 *sobre els drets d'informació concernent la salut i l'autonomia del pacient, i la documentació clínica* (Patient's right regarding their health and autonomy and clinical records)
- Spanish law, Ley 14/2007 Investigación biomédica, regarding the biomedical research.

Moreover, as medical devices become more sophisticated, cybersecurity becomes a growing concern. The IS0 27001 is the one that includes the requirements for the insurance of data security. The growing market for smartphone-based health monitoring applications, as well as connected devices in the diagnostic, require proactive information security standards. Added to this, is the risk of intellectual property being compromised in the event of an information leak, which is why ISO 27001 has become a vital standard for medical device and healthcare manufacturers.

## 5. Concept engineering

The idea is to perform a monitorization of the patient's different biological parameters and perform a prediction on whether these patients will develop an hepatic encephalopathy without preventing them from having a normal life. Since the TIPS procedure is a minimally invasive surgery, the patient only needs to stay a night in the hospital to ensure there were no complications with the procedure and that the pressure in the portal vein has dropped correctly.

Although the patient can lead a normal life very shortly after the TIPS procedure, that does not exempt him from suffering from hepatic encephalopathy later on. Therefore, in order for the patient to agree to wear medical devices that monitor their biological parameters for life or until the liver condition is fully treated, this should be non-invasive and unobtrusive, allowing the patient to move freely and without discomfort. Moreover, these biomarkers or biological parameters must be continuously registered and checked.

However, since this is a very extensive project, as mentioned earlier, we have centered our project on the study of biological ions such as ammonia and others that can have a correlation with the development of HE. Therefore, taking into account the aforementioned points made about the patients' situation and focusing on ion-detection, the following possibilities were studied.

### 5.1. Ammonia detection

First, since the main parameter proven to be a biomarker for HE is ammonium, $NH_4^+$, it was imperative to study a way to monitor it continuously for a relatively long period of time. As mentioned earlier, at present, when diagnosing a HE, the ammonium blood levels are obtained invasively using a blood sample and cannot be measured continuously.

#### *5.1.1. Skin-sweat patches*

Currently, $NH_4^+$ can be measured from blood, sweat or urine samples. Since there is a proven relation between the ammonia in blood and sweat levels, and in the medical market we can find skin-patches able to measure the concentration of certain ions from a sweat sample, the idea of measuring the ammonia from sweat was contemplated [6]. Using urine samples to measure $NH_4^+$ concentrations was discarded due to the lack of studies proving a relation between the urine and blood $NH_4^+$ concentrations and because this way we cannot make continuous measurements. Moreover, skin-patches have the advantage of being comfortable and unobtrusive while urine $NH_4^+$ detection would involve the patient to provide urine samples in short periods of time.

### 5.2. Study of other possible biomarkers

As mentioned earlier, nowadays, besides ammonia, there are no biomarkers that have been proven to be related with the risk of developing an HE. Therefore, this same project will aim to find out if there are other biomarkers that can be related to the disorder. As we decided that sweat would be the body fluid that we would be using and we were targeting $NH_4^+$, which is an ion, we hypothesized that we could use the same technique in order to detect other biological ions.

As the chosen technique for detecting NH4+ concentrations is an ion-selective potentiometric cell using sweat as the biofluid, we studied what was sweat composed by and tried to find if any of these components had a clinic relevance regarding liver functioning or hepatic encephalopathy development.

Perspiration consists of water, minerals, lactate and urea; minerals mainly being sodium (0,9g/L), potassium (0,2 g/L), calcium (0,015g/L) and magnesium (0,0013g/L). [17] Considering that all the minerals mentioned were ions, a potentiostat could be used in order to assess their concentrations in the sweat of the patient. Hence, we studied thoroughly each ion and its possible correlation to hepatic encephalopathy. In the following sections, the ions chosen and its clinical relevance regarding the studied pathology have been discussed.

#### *5.2.1. Sodium*

When studying the clinical relevance that the sodium ion has on the liver, we found out that hyponatremia is the most common electrolyte disorder in patients with secondary to advanced cirrhosis and portal hypertension. This parameter is even considered an important prognostic marker both before and after liver transplant for patients suffering from cirrhosis [18]. In the case of cirrhotic patients, the hyponatremia can develop as an increase in extracellular fluid volume and in the absence of major sodium losses, which is known as dilutional or hypervolemic hyponatremia [19].

Moreover, some studies also show evidence suggesting that hyponatremia may affect the brain function and predispose hepatic encephalopathy. At first, although there is a lack of studies assessing neurological symptoms in cirrhosis with hyponatremia, clinical experience indicated that there is a relatively low incidence of neurological manifestations in patients with cirrhosis that could be due to the fact that these patients have chronic hyponatremia rather than acute and, hence, the brain has enough time to adjust the hypo-osmolarity of the extracellular fluid.

However, a new hypothesis developed, proposes a role for a low-grade cerebral edema in the pathogenesis of hepatic encephalopathy [20]. According to this new hypothesis, ammonia and other neurotoxins act symbiotically increasing the intracellular content of glutamine (related to ammonia metabolism), causing the swelling of astrocytes and inducing a low-grade cerebral edema. This astrocyte swelling would result in numerous alterations of the neurological function, which would facilitate the development of HE. In this context, hyponatremia could represent a second osmotic hit to astrocytes, which could no longer activate any osmotic counteractive systems. In this case, cells would not be able to tolerate any other cell volume issue and HE would develop because of any other osmotic stimulus [20]. *Figure 2* shows a scheme of the aforementioned hypothesis regarding the role of hyponatremia.

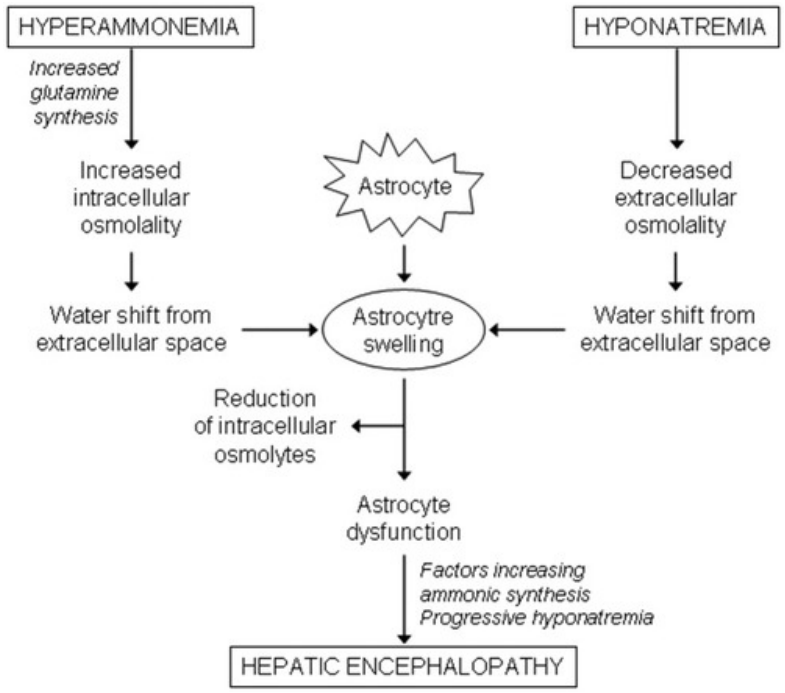


***Figure 2.*** Proposed interaction between hyperammonemia and hyponatremia and possible relationship with hepatic encephalopathy scheme [20]

Discussing this ion relevance with the specialists working in the Hepatic Hemodynamic unit, it was concluded that would be a of interest to include this ion in the study since it is also considered a possible triggering factor for the triggered-type of HE and would be interesting to study whether it could be a predictive factor for spontaneous HE as well.

*5.2.2. Potassium*

The role that potassium has on the facilitation of HE development is unclear. While there are studies that hypothesize that hypokalemia has an indirect impact on the apparition of an HE episode, other studies hypothesize that hyperkalemia might be a protective solution since it destabilizes the acid-base balance unfavouring HE.

On one hand, it is though that hypokalemia in HE is modulated by the kidney since, as less potassium reaches the collective tubules, more hydrogen ions move into the cells, thus, creating a state of relatively intracellular acidosis. Therefore, the kidneys are forced to generate more ammonia, among others, in an effort to balance the acid-base homeostasis of the patient. They do this by increasing the levels of ammonia, which are strongly associated with HE [21].

On the other hand, it is also discussed the effect that hyperkalemia, and not hypokalemia, diminishes the risk of suffering from HE, therefore studying low levels of potassium could become also a predictive factor. There are two main hypotheses: hyperkalemia decreases total ammonia production in the proximal tubule by increasing the pH homeostasis impairing ammoniagenesis and that since potassium competes with $NH_4^+$ for absorption, it is reducing the ammonia accumulation in the medullary interstinum so that there is less ammonia available for absorption in the systemic circulation.

Since it is known that electrolyte derangements commonly precipitate HE events, it would be interesting to also study the possible relation that this ion concentration has to HE. However, there is small prove or studies that can correlate o hypothesize and thus, it is very unclear if the use of this parameter can provide any relevant information regarding HE.

*5.2.3. Lactate*

Lactate is one of the substances produced by cell metabolism, with the highest level of production occurring in the muscles. Depending on the pH of the body, the lactate is sometimes present in the form of lactic acid. A change in pH influences the lactic acid levels and also lactic acid levels affect pH. It is widely known that elevated lactate is sign of infection, however, there is also a hypothesis that correlates elevated lactic acid levels with a facilitation of HE development.

Additionally, the relationship between of pH, ammonia and lactate with the HE pathogenesis is unclear due to its complexity. It is unresolved whether an increase in cerebral lactate is correlated or not to ammonia leading to astrocyte swelling and acidosis. However, it is suggested that an

increase of lactate in the brain, occurs in association with the progression and severity of HE being unclear if it is caused by this substance. It is inconclusive whether if one of the components mentioned or the combination of three are implicated in the development of HE [22].

To sum up, an increase of lactate in the brain might not only be a consequence, which would consider it a biomarker, but a cause of the HE pathology. When discussing the addition of this parameter with our medical consultors, it was decided that, even though there were not many medical evidences of its relation to HE, it would be interesting to add this substance to the study since it was proven to have a correlation with infections together with pH and C-reactive protein.

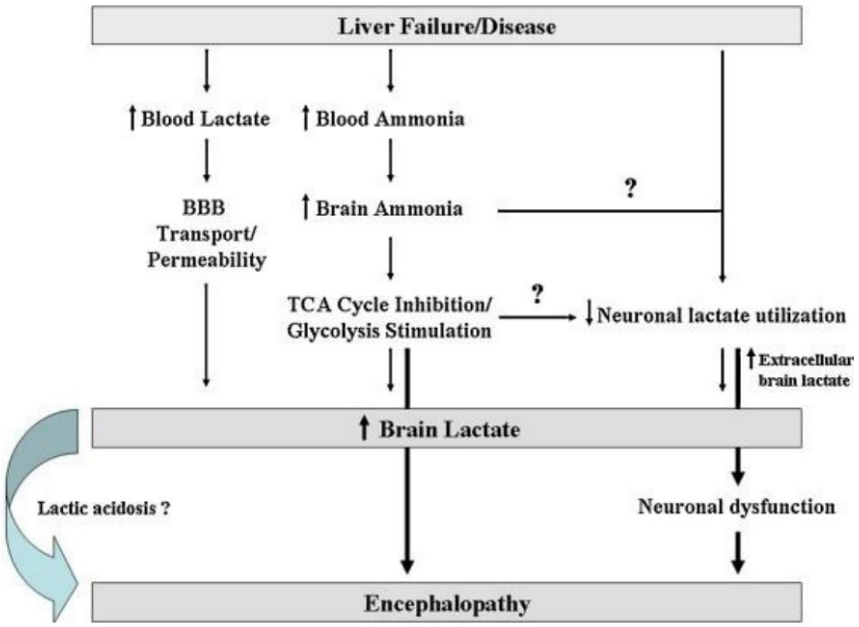


***Figure 3.*** Schematic summary describing the possible causes of increased brain lactate and its role in the pathogenesis of hepatic encephalopathy [22].

*5.2.4. Calcium*

The role that calcium has on the development of HE is very unclear and complicated. Directly, there is no clinically proven relation between the pathology and this ion. However, as mentioned before, elevated levels of ammonia are consistently found in patients with HE and astrocytes swelling appear to be the principal neural cells that are affected by ammonia toxicity. The previous statement is relevant because calcium, is shown to have a transient rise as the earliest events when astrocytes exposed to ammonia [23].

Although this ion was chosen due to its concentration in perspiration, discussing this ion with the medical experts, there was no apparent relevant clinical relation yet known and, therefore, it would be discarded.

### 5.3. Biomarkers proposed for the study

After performing an exhaustive analysis of the clinical relevance of the aforementioned ions that are present in sweat, we have augmented which ones are the ideal to add as biomarkers to monitor in this project.

After consulting the proposed ions with the clinical experts working on this project, they argued that, although as many of these ions would be interesting to study since there are no previous studies regarding its clinical relevance and might be of interest, both lactate and sodium had the most clinical relevance regarding the appearance of HE. The sodium was chosen to be studied since it is considered a possible triggering factor for the triggered-type of HE and lactate was chosen due to its use for infection diagnostic, which is also considered a triggering factor for the triggered-type of HE.

Although potassium seemed to have a relation with the development of HE through ammonia and would be used to predict with time if ammonia levels could be risen due to low levels of potassium, there is not enough studies and bibliography that support with clinical evidences the stated hypothesis and also it is not a common ion studied with perspiration, so there are not many studies or projects performed with potentiostats published.

Finally, calcium was, as well, not considered in this project since it is not related to HE directly but its rise is caused by ammonia toxicity and astrocyte swelling. Therefore, the increase of ammonia levels in not dependent on calcium and only but studying the levels of ammonia we would obtain the same information. Moreover, there are practically no studies that relate it to ammonium and it seems to be a very little studied field.

## 6. Detail engineering

In this section, it will be explained in detail the design of a biosensor prototype that will be used to measure the previously mentioned ions and also all the considerations that have been taken into account when designing it.

In order to solve the current need for sweat ammonium detection for patients that are not performing a physical activity and that are only used for a very short period of time, we have designed and conceptualized our own ammonium detector that consists of a point-of-care (POC) device.

Since it is addressed for patients that have a cirrhotic liver but that are having a normal life at home, our design consists on a thin sensor that would be stuck on the back of the patient, since it is a good location to perform sweat analysis and it does not limit the patient's movements. According to the World Health Organization (WHO), the development of portable POC diagnostics requires that the characteristics of the acronym ASSURED (affordable, sensitive, specific, user-friendly, rapid and robust, equipment free, and deliverable to users) are covered.

Therefore, we aim to design a POC device able to continuously measure ammonia concentration using sweat as the biofluid to analyze. Moreover, it is intended to follow all the previously mentioned characteristics and improve its lifespan, facilitating its use.

### 6.1. Conceptual design and initial requirements

In this section it will be explained the disposition of the different blocks that compose the biosensor and how they are connected among them. *Figure 4*, shows the design and the disposition of the aforementioned blocks that will make up the biosensor. Additionally, the arrows drawn in the draft represent the connection that each block has with the rest of blocks in the sensor.

As it can be observed in the previous figure, the biosensor designed is divided in four different blocks, which are:

- **Sensor**: part in charge of measuring the targeted analyte concentration. In this block there is the receptor where the biofluid to analyze will be kept and the electrodes that will sense the targeted analytes. It is connected to the control/electronic block since the later will transduce the signal obtained. Moreover, it is also connected to the power source.
- **Power**: most or all blocks from the biosensor need to be powered in order to do their tasks. Although later it will be discussed how the system will be powered, it is important to notice how this block is connected unidirectionally with the rest of the components. The dashed

lines that connect the electric/control block to the power block and the later to the sensor, indicate possible improvements or discussions that will later be explained.

- **Electronic / control**: part in charge of transducing the signal obtained by the sensor and received from the detector. It amplifies the biochemical signal and alters the resulting signal into electrical. Since the measurements performed by the sensor are obtained as voltage, this block will also be in charge of computing a conversion from voltage to mM (concentration of the analyte).
- **Communication**: part in charge of sending the results obtained when sensing the analytes to an external computer system. Therefore, it is connected to the electronic/control block and to the power block, since the results that will be transmitted come from the electrical block and it needs to be powered in order to send the data.

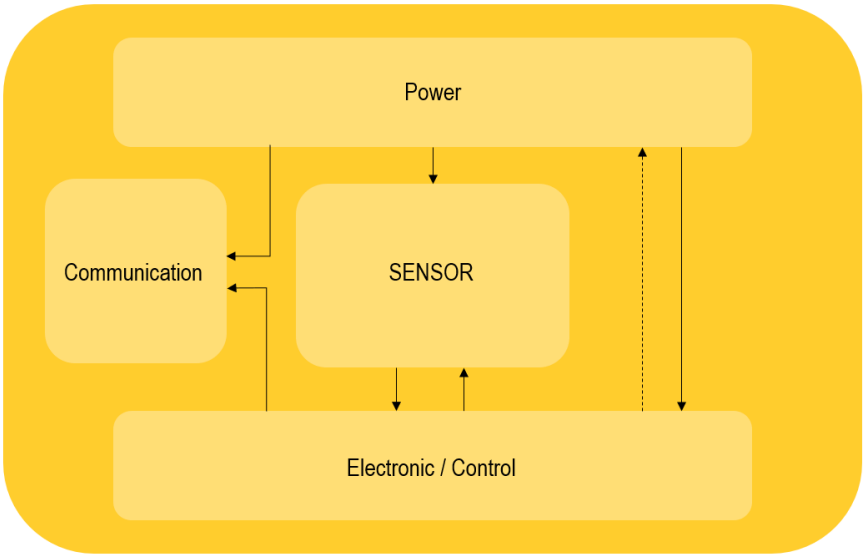


***Figure 4.*** Scheme of the location and connection of the different components.

Once all the blocks have been explained, we will conceptualize and explain the design of each block individually.

### 6.2. Sensor

In this section we will discuss the sensor block, which is the part that is in direct contact with the biofluid that will be analyzed. It will be explained the measurement mechanism chosen and the specifications of the sensor block.

There are different types of sensors that can measure concentrations of an analyte in sweat samples, which would be, for instance, optical, impedance-based and electrochemical. However, the chosen type was an electrochemical sensor, which is the one used in sweat ion-detection and has also gained relevance the last few years due to their high specificity, low cost and commercially available materials [24].

The aim of an electrochemical sensor is to give information about the composition of a substance by coupling a selective layer to an electrochemical transducer. It uses an electrochemical cell with electrodes of different dimensions and possible modifications. Generally, it uses three kinds of electrodes, which are the working electrode (WE), the reference electrode (RE) and the counter or auxiliary electrode (RAux). Inside the electrochemical category, there are three different types of sensors, which are amperometric, potentiometric, impedamentric and voltammetric which depend on the signal obtained.

The most common methods of detection used in sweat analysis are *enzymantic amperometric* and *potentiometric ion-selective electrode (ISE)* sensors. However, the first one is used for metabolite sensing, such as lactate, and uses biosensors with enzyme recognition elements. The second one, potentiometric ion-selective electrode, was the chosen since it is the one used to detect electrolytes, such as $NH_4^+$ and $Na^+$, which are the analytes we are interested on. [25]

*6.2.1. Ion-selective electrode (ISE)*

The potentiometric sensors incorporate only two electrodes: the working electrode (WE) and the reference electrode (RE). They measure their relative electrical potential when there is no voltage present and use ion-selective electrodes (ISE) to transduce the biological reaction into an electrical signal, which are the typical potentiometric sensor for selective ion recognition [26].

The ISEs are transducers that convert specific ion activity into a readable signal. They use the Nernst equation since the logarithm of the target ion activity can be related to the difference of potential existing between two sides of a membrane that only allows the passage of the targeted ions [25].

ISEs technique presents many advantages compared to other electrochemical techniques, including [27]:

1. It is inexpensive and easy to operate with.
2. It has a wide concentration measurement range; therefore, it is able to measure very low ion activity.

3. As it measures the activity, instead of the concentration, it is particularly useful for medical applications.
4. It can perform real-time measurements, meaning that it can monitor the charge of the activity of the ion through time, allowing a continuous monitorization of the ions.
5. It can be used to determinate the activity of both positively and negatively charged ions.

Considering all the advantages that this technique has regarding ion detection and that it has already been proven to work relatively efficiently for other biological ions, it was decided that this would be the technique used in this sensor to study the sweat ammonium concentration.

The main characteristic of the ISE is that they have a membrane that only allows the have a membrane that only allows the passage of certain ions depending on the membrane material, which is specific for each ion. This membrane is also a method to classify the different ISES, which are: solid-state membranes (fixed ion exchange), liquid membranes (mobile ion exchange) and membranes in special electrodes [25].

However, there are a few drawbacks for this technique related to this selective membrane since the truth is that there is no such membrane that only permits the passage of one ion. Depending on the membrane used, other non-targeted ions could pass through it affecting the measured potential. Additionally, it is important to notice that since it has an ion-selective membrane, one ISE is only suitable for one type of ion, which might be inconvenient in our project initial where we intended to study as many ions as possible.

Regarding the materials for the electrodes, in our case, after reading several papers on sweat-ion detection, it was shown that the working electrode that was usually used for sweat analysis was fabricated by inject printing of a gold nanoparticle ink onto a PEN (polyethylene naphthalate) substrate [24]. On the other hand, the reference electrode consisted on Ag/AgCl ink [24, 26, 28], screen-printed onto the same substrate. This substrate was presented in some articles due to its conformability to the skin and its ability to withstand the sintering temperature of gold nanoparticle ink (250 °C) [24]. From all the research performed, these electrodes were chosen because the papers that studied the ammonium detection using the aforementioned electrodes showed promising results. Moreover, some studies [24] have also shown that combining ion-selective ionophore solutions drop-casting them into the sensing electrode improves the performance of the transducers since they reversibly bind $Na^+$ or $NH_4^+$ ions.

The final aspect that needs to be considered is that biofouling influences selectivity, meaning that a prolonged contact of the sensing layers with the chemical species will produce an accumulation

of the later that will gradually degrade the sensor performance over time. Therefore, we have designed a system that will prevent that from happening that will be explained in detail in the power section.

### 6.4. Electronics/control

For many sweat sensors prototype, signal transduction occurs at the sensing component while signal conditioning occurs in the electronic component. This is the case we have proposed, where we have used the ISEs as transductors. Therefore, in this module, we will discuss a little bit the signal processing part and the ADC and the microcontroller components.

It is important to highlight that this model, referring to the transducer being on the sensor block, is only effective when the signal amplitudes are large enough that the transfer between the sensing component and the signal processing block does not produce a significant attenuation or adds noise to the signal, which would apparently be our case although it would require to be tested. [29].

Filtering raw sensor signals in order to eliminate the noise, is the main role that the electronic components have. This noise obtained with the signal might come from the patient's movements that alter the connectivity and impedances in the interface between the sensing component and the analyte substrate. Therefore, low-pass filters to remove the noise from motion, which usually appears as high frequency noise [29].

As mentioned early, the electronic backbone of this device consists of the aforementioned analog front-end that will improve the quality of the sensor signal and also it comprises an analog to digital converter (ADC), and a pre-programmed microcontroller that will calibrate the signal from potential to concentration values.

*Figure 5* shows a block diagram of the connections between the different components of the electronic block system. As observed, the power block is connected to the PMU (Power Management Unit) where it is managed and also to the signal processing block that uses amplifiers in order to process the signal and they need to be powered in order to do so. Additionally, the sensor, which consists on the potentiometer that measures a signal proportional to the concentration of ammonium, is sent to the signal processing will the signal will be amplified and noise will be removed. Both the PMU and the signal processing block are connected to the Control and Processing Unit (CPU) that will convert and process the received information and sends it to the communication block, where the measurements will be sent to an external phone or computer.

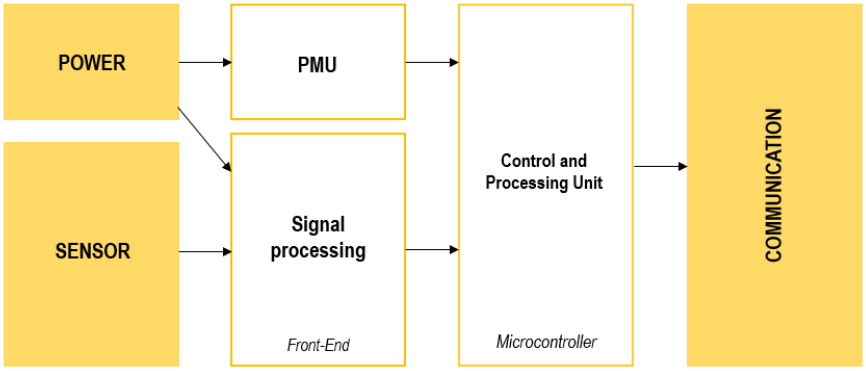


***Figure 5.*** Block-chain of the different components of the electronics system.

Furthermore, in order for the microcontroller to perform the calibration, we need to obtain a calibration curve from previous papers that have used the same electrodes and methods to obtain the electrical signal. Although one-point calibration* will be necessary to account for baseline differences in the obtained signals, a universal calibration curve ensures that only one preliminary measurement will be required [29].

The following figure, shows the results obtained from the practical experimentation of a sweat ammonium sensor that used the same type of electrodes that we used. Using this plot, we can compute the relation between the potential and the ammonium concentration and, therefore, obtain the calibration curve.

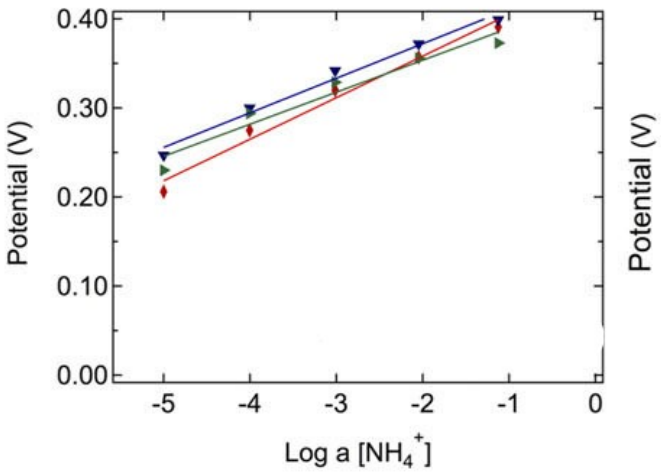


***Figure 6.*** Calibration curves of the NH4+ sensing electrodes [24].

Moreover, besides being able to compute the calibration from the previous figure, we can also observe the range of voltage that we need to measure. Apparently, looking at the previous figure, we can conclude that the voltage range would be from 200 to 500 mV.

It is also important to specify how often do we have to measure and transmit the results. Since what we want is to monitor the ammonium continuously, we would send the measurements at lest once a minute.

### 6.3. Power

In this section we will discuss the power block, which is the part that powers the rest of the blocks. It will be discussed how the device is power considering its function, commodity for the patient and the state of art for biosensors point of view.

Minimizing power consumption is a key consideration when developing wearable that operate continuously for longer periods of time. Therefore, it is important to understand where power drain is dominant in order to choose the ideal components for the design that will make consumption minimal. In a sensor, the power consumption is dominant in the modules where the op-amps are included, since they need to be inputted a current in order to amplify a signal, which consume a few mW always depending on the exact circuitry designed. Moreover, similar amounts of power are drawn by the ADC and the microcontroller. Additionally, the transmission component that will be used to communicate the data to an external computer, is the one that dominates power consumption and, later, it will be discussed which is the best component to improve the consumption [29].

We need to consider that the aim of our biosensor is to make continuous measures of an analyte for a very long period of time. It would be used until the patient had a transplant that would change their liver condition or until the patient died, considering that the patient's health is very deteriorated.

Initially, it was proposed to use a fuel-cell to power the system, which consists of using the substrate that is being sensed to power the electronic system. This would seem to allow us to have a non-ending power-supply since we would always have this biofluid, however, this is very new technique that have some drawbacks. The main ones would be that it would increase exponentially the price of the device and that, since this field is still being developed and improved, there might be some meaningful errors in the readings. Also, the power supply that this Moreover, it takes up a lot of space of the sensor and, since we want it to be simple, small and elastic, we have decided that is not the best choice.

Additionally, we could use the conventional batteries that most biosensors use, for example, li-ion batteries or thick-film batteries based on lithium. However, regardless of their autonomy, these batteries need to be changed periodically to maintain the device operating. Moreover, as discussed

earlier, since the sensor part also needs to be changed to avoid biofouling, we have proposed a solution inspired on the “Plug-and-Power” [30] that consists on designing a mobile piece of the sensor that could be changed easily and that contained only the power and the sensor blocks. Therefore, the rest of electronics would remain the same reducing the waste of the components. *Figure 7* shows a scheme of what the sensor path would look like.

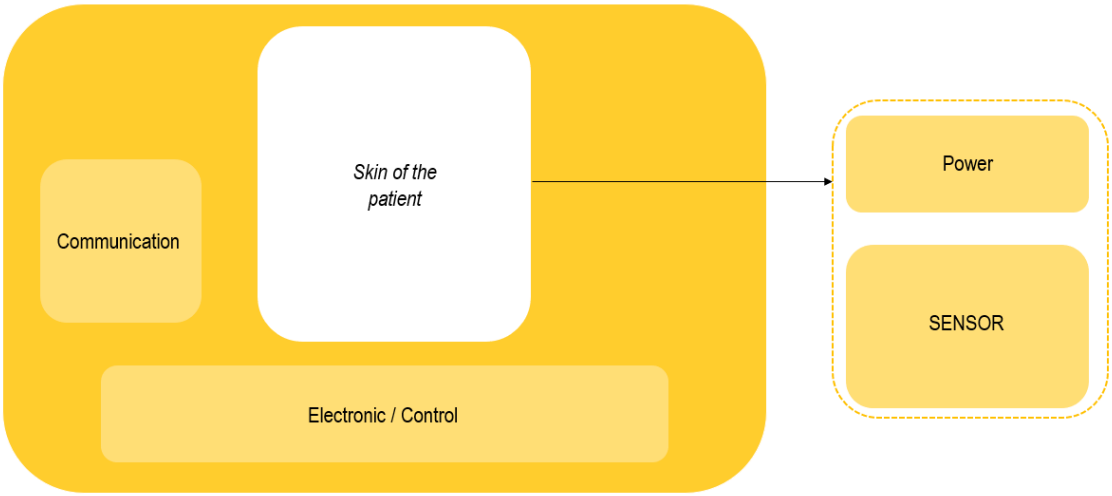


***Figure 7***. Scheme of the plug-and-power device designed.

The proposed solution would be use lithium ion batteries, that due to their particular high energy and their density, are used for small devices that require long-lived batteries, which is the current case for most sensors and medical implants.

### 6.5. Communication

In this section, we will discuss how the measurements obtained will be sent to an external computer or mobile device where they can be visualized. Different aspects of the method that will be used have been assessed considering their power requirements, distance and security.

Among the discussed methods, we have WIFI and Bluetooth. The first one was discarded due to the fact that it is energetically inefficient. Therefore, the Bluetooth option was studied more thoroughly. The Bluetooth transmission component requires around 30 mW to work, dominating the power consumption of the device [29]. An option was to directly show the sensor readings on the device using a display, which would be very energetically efficient but it would prevent the data accumulation, the contact with the healthcare personnel and would force the patient to continuously be checking the device for information.

Some alternative proposed in order to diminish the power consumption was the *Near-field communication (NFC)*, which enables the data transmission without the need to power the transmission components within the sensor itself. It uses power from the receiving device to trigger the measurement and data collection. However, its main inconvenient is that it requires a much shorter range of interaction between the device and the receiving phone [29]. This would not allow a proper continuous and autonomous sensing without having always the receiver close to the sensor and will limit the patient's mobility. Hence, this alternative was also discarded.

Another method that biosensors usually use to avoid high power consumption when sending the measurements is to perform a periodic transmission in which the device alternates between data transferring and low-power states which will allow a semicontinuous analyte readings. This method could be applied in our case since, depending on the rate of the readings, changes on ion concentrations are not immediate.

Finally, the new technology called Bluetooth Low Energy (BLE) was assessed. This method was designed for continuous data transmission applications, which means that a lot of data can be exchanged over short distances. In Bluetooth Low Energy networks, devices can be either central or peripheral. Central devices, in our case smartphones, have more processing power and are responsible for controlling peripheral devices. Central devices generally run software specifically created to interact with peripheral devices, which serve as sensors that collect data and send it to central devices for processing [31]. The key to low power consumption is that they do not process data, they only collect it. Since this method is extremely useful in medical devices, this was chosen to be used in our device.

Since BLE was the chosen method, it is important to notice that the distance at which data can be transmitted is much shorter than the distance to the medical specialist. Therefore, the data will be sent to the patient's mobile phone and, from there, the results will be sent to the doctor or the patient will simply be alerted when the ammonium levels are elevated.

### 6.8. Design conception

To sum up, we have created the following table that contains the main characteristics decided for this sensor and explained in the previous sections.

| DESIGN SPECIFICATIONS | |
|---|---|
| **Species that analyses** | Ammonium ($NH_4^+$) |
| **Type of sensor** | Potentiometric |
| **Electrodes used** | Ag/AgCl ink on PEN (RE)<br>Gold nanoparticles on PEN (WE)<br>Extra layer with ion-selective ionophore. |
| **Voltage range needed to measure** | At least from 200 to 450 mV. |
| **Battery** | Plug-and-Power system |
| **Communication** | Bluetooth Low Energy |
| **Dimensions** | 1 x 1 x 0.25 cm |

***Table 1.*** Main characteristic of the sensor.

## 7. Technical viability

In this section of the document, it has been not only explained the technical specifications and principal features regarding the eventually designed prototype but also a SWOT analysis was performed studying its corresponding strengths, weaknesses, opportunities and threats. Hence, the project has been evaluated as a potential marketable product that could be developed in the following years and could be improved in the future with further investigations regarding the medical devices explained in the market analysis section.

### 7.1. Technical specifications

In this section, the technical information concerning the biosensor prototyped that was designed in the previous section will be exemplified in *Table 2*. This table follows the World Health Organization (WHO) user guide for medical devices template.

| NAME, CATEGORY AND CODING | |
|---|---|
| **Generic Name** | Sweat ammonium ion-detection device |
| **Keywords** | Sweat analysis, biosensor, ammonium, hepatic encephalopathy, continuous. |
| **PURPOSE OF USE** | |
| **Clinical or other purpose** | Capability of continuously measuring the ammonium concentration is sweat. |
| **Level of use** | Home |
| **Clinical department/ward** | Hepatic Hemodynamic unit |
| **Overview of its functional requirements** | It is required to measure with precision subtle changes in the ammonium sweat concentration continuously and transmit the measurements to an external device. |
| **TECHNICAL CHARACTERISTICS** | |
| **Detailed requirements** | It is required to be able to work with a voltage range from 200 to 450 mV. It needs to be calibrated before its use and it requires external components that will be used to change the substrate where the sweat will be analysed and the batteries. |
| **Display parameters** | Ammonium concentration and reference values alerting whether if the value if high. |
| **PHYSICAL/CHEMICAL CHARACTERISTICS** | |
| **Mobility, portability** | Since it is a wearable device, the patient will have it on them, ideally on the back since it is |

| | |
|---|---|
| | easier to obtain sweat samples. It will not limit the patient's movement or be uncomfortable since it will be wireless. |
| **Raw materials** | Electrodes coated with gold nanoparticles and Ag/AgCl ink on PEN. |
| **UTILITY REQUIREMENTS** | |
| **Electrical, water and/or gas supply** | Lithium battery. |
| **Consumables / reagents** | An external component of the sensor will consist on the sensing part and the batteries that will be changed regularly. |
| **DECOMISSIONING** | |
| **Estimated Life Span** | Patient's life span. |
| **SAFETY AND STANDARDS** | |
| **Risk classification** | Class 2b |
| **Regulatory approval/certification** | CE (European) and FDA (American) |
| **International Standards** | ISO 13485, IS0 10993, ISO 27001, ISO/IEEE 11073, ISO 14971. |
| **Regulations** | Organic Law 15/1999 on the Protection of Personal Data, Llei 21/2000 *sobre els drets d'informació concernent la salut i l'autonomia del pacient, i la documentació clínica* , Ley 14/2007 *Investigación biomédica*, regarding the biomedical research. |

***Table 2***. Technical specifications of the designed device

### 7.2. SWOT Analysis

As in any other project to be brought to market, it is important to study its strengths and weaknesses (internal factors) and its opportunities and threats (external factors) related to business competition or project planning. As explained in the "market research" section, there is currently an urge to develop new biosensors based on sweat-analysis and an increasing number of projects and companies are getting started on this field. Therefore, it is important to perform a SWOT analysis examining all the factors regarding the technical viability of this project in order to build on the positive factors and address the negative factors thus, minimizing risks and taking possible advantages to increase the chances for success.

### *7.2.1. Strengths*

From the complete project point of view, the implementation of a device able to predict HE in a non-invasive way and at home it will satisfy a real need and not only improve the quality of life of the patient but also safe time for the doctor who will not need to perform additional tests when the patient arrives to the hospital.

Additionally, this project presents an opportunity to discover new unknown factors that also affect the incidence of HE and discard the ones that do not have any correlation with the pathology. Hence, this project will not only pose as a solution to diagnose more efficiently the pathology but also will be used to perform a thorough study on other possible biomarkers for HE.

Another strength worth mentioning for this project is the fact of working together with the Hemodynamic Hepatic unit of a reference hospital such as the Hospital Clinic, which has very experienced team and allows the project to have also a healthcare point of view.

### *7.2.2. Weaknesses*

There is a lack of papers and bibliography regarding sweat sensors since it just gained relevance as a medical product a few years ago due to technology improvements in the sensorics' field and, therefore, there is also a very few experts on this field.

Additionally, this is a very hypothetical project that has not been yet implemented not tested and, considering the medical regulations, will not be implemented for a few years. Therefore, the real functioning and performance of the designed biosensor has not been corroborated. Moreover, due to the aforementioned healthcare regulations, the cost of materials and manufacturing could strongly rise.

### *7.2.3. Opportunities*

This project is focused on patients that have a cirrhotic liver and require a TIPS implantation in order to increase their life conditions. Each year, only in Spain there are more than 400 TIPS procedures performed, therefore, it has a strong market base.

Since biosensors is a very new field, there are not many consolidated companies yet that are aiming to create a biosensor that detects the concentration of ammonium in patients that may develop an HE, hence, there is a great opportunity to expand in this market sector.

Moreover, in the case of the proposed biosensor, since it aims to monitor, non-invasively, the ammonium concentration in sweat, its use is not restricted only to the diagnostic of HE and could be used to work as a complementary test for many other pathologies, having more opportunities of expansion in the market.

*7.2.4. Threats*

There are two main factors that this project could be threaten by. The first one is the restricted commercialization that our product could have due to the strong regulations and legislations that need to be met and the fact that they are continuously changing as medical technology evolves. The second one is regarding the increasing market competition that there will be in the future since biosensors and point-of-care devices are increasingly being investigated.

Finally, in order to graphically exemplify all the aforementioned information, a diagram corresponding to the SWOT analysis for this project was performed, observe *Figure 8.*

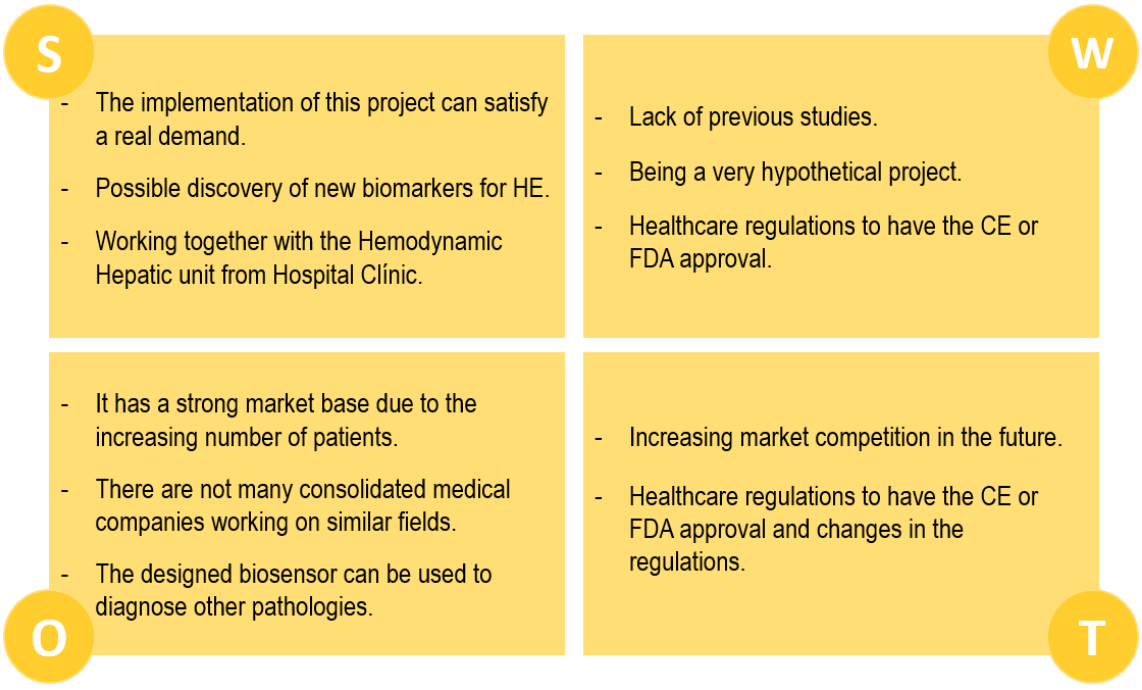


***Figure 8.*** SWOT analysis of the project.

## 8. Economic viability

In this section, we will study the economic viability for this project despite the fact that the designed prototype that has been exposed in this project it has not yet been implemented and, therefore, there was no budget for its development.

It is very complicated to estimate a price, since all the similar devices to which we could compare our device are only written on papers and are not yet available in the market. Therefore, the price of this device cannot be estimated. Nonetheless, we could consider the cost of hiring both a biomedical engineer and an electronic engineer that would work together the conceptualize the device, which would be the job of the first one, and to design the electrical components inside the sensor such as the noise filters or the signal amplification, which would be the job of the second one.

Considering that 15€/hour could be a suitable salary for recent biomedical engineer and electronical engineering graduates, and that the period of time for developing this device could be of 300 h (around 2 months), the budget that we could consider for this project is of 9,000€.

Moreover, considering that the final setup of this project has the intention of solving a notorious problem, since last year there were 42 patients that had a TIPS implanted just in Hospital Clínic and over 400 patients in Spain, it would have a strong potential market base. Additionally, this type of sensor could be used for other pathologies which would increase even more its potential revenues.

## 9. Execution chronogram

In the following section, the temporal organization of the different tasks that have been performed to achieve the goals set for this project will be explained. Graphic representations have been used to clarify and to have an easier understanding of the various tasks and timings.

It is important to mention that, since it was a very innovative project, we did not follow any linear tasks. A possible solution was studied and, if it had a chance to be used it was followed through and, if it had issues that could not be solved, such as the fact that the technology is not yet at this stage of development, we would go back to the beginning and propose another solution. Therefore, some periods that are very extend also correspond to the decision-making stage mentioned.

### 9.1. Phases and milestones

This project could be divided into different main parts or tasks, each one having a principal milestone to achieve. These phases or milestones are the following:

- *Research stage*: this consisted on the first stage where we were familiarized with the HE development, its possible causes and its diagnosis. Moreover, a research of the market was performed in order to understand what other techniques that were currently available could be applied in our project. Finally, at the end of May, we performed a clinical immersion that was later useful for the logistics design of the project.
- *Project design stage*: designing and ideating the overall project proposed considering the type of patients, the market analysis and the symptoms studied in the previous stage. Clarifying which are the requirements for the project and studying the overall viability of the project. Moreover, since we decided to focus on the ions as biomarkers, a study was performed in order to decide which ions present in sweat could be used in this project.
- *Biosensor design*: since it was decided to focus on the ion detection using sweat, a biosensor able to measure the ammonium concentration in sweat was designed. To do so, the global design of the sensor was proposed as well as its concrete components and the connections and structures that it would have.
- Project memory: section where the suitability of the overall project and the designed prototype was evaluated and discussed and the memory of the project was written and presented.

### 9.2. Definition of tasks and timing

First, the following figure, which shows the Work Breakdown Structure and WSB dictionary for the project has been used in order to clarify the different tasks, responsibilities and milestones of the project.

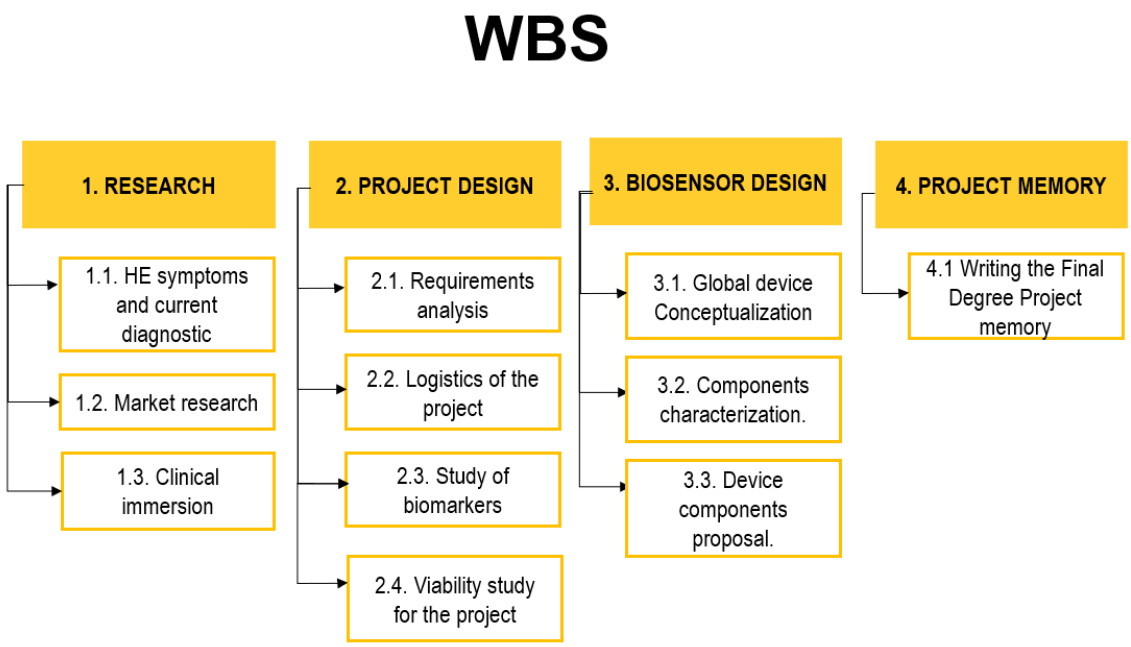


***Figure 9.*** WBS of the project.

The tasks and the required timing for the correct development of the project are the following:

*Research stage*

1.1. **HE symptoms and current diagnostic**: this task implied the familiarization with the HE pathology, its symptoms and the current diagnostic techniques that were studied bibliographically and also using the knowledge provided by the associate doctors of this project during our online meetings. This project lasted about two months, although it was not the only one being performed at that time, since there is a lack of information regarding the exact HE causes.

1.2. **Market research**: a bibliographic research on the currently available products that could be related to our project was performed. It was shown that there are no specific devices designed that predict HE. Moreover, most of the technology that could be applied in our project is still being studied and developed and it is only found in research papers. This task was also performed during two months simultaneously with the previous task and was performed several times since we encountered many dead-ends.

**1.3. Clinical immersion:** on late May, a visit to the Hemodynamic Hepatic unit in Hospital Clinic was performed, where we were able to observe the procedure of a TIPS implantation and where clinical doubts regarding the study biomarkers were solved. This visit was performed late, however, as it is included in the research stage and it is presented as such, the GANNT diagram may vary a little.

*Project design*

**2.1. Requirement analysis**: in order to design a useful project, we had to perform a requirement analysis that studied the necessity exposed in this work and the scope that this project could have. We defined how to focus the project and how this would be developed.

**2.2. Logistics of the project:** a logistics analysis was performed in order to consider the patients' and the medical physicians' point of view and requisites. In this task the patient's condition, mobility, post-operational and lifespan were considered.

**2.3. Study of biomarkers**: once the research on HE was performed, we decided that we would focus our project on ion-detection since ammonium was the only biological sample used to diagnose HE. Since high levels of ammonium were not exclusive for HE, bibliographic research was performed in order to study the correlation that other ions, present in sweat, could have with the development of an HE in order to include its detection in the project.

**2.4. Viability study of the overall project:** this task consisted on studying the viability of the project this being conceptual, in economic terms or in technical terms. Moreover, it also included a study of the European current regulations regarding medical devices and the standards and requisites that might have to be fulfilled. This task lasted approximately two weeks and depended on the logistics and focus of the project chosen.

*Biosensor design*

**3.1. Global device conceptualization**: this task was performed with the help of Dr. Jordi Colomer from the Biomedical Engineering department. A meeting was performed where an initial draft of the biosensor was drawn and the basic characteristics and dispositions of the elements in the sensor were discussed.

**3.2. Components characterization**: the two following weeks to the previous task, consisted on designing exactly each module or block in the sensor studying, for each part, which would be the best method to sense the samples, the signal processing needed, power consumption issued and the communication protocol and how would these modules be connected between them. An amount of two weeks was set to perform this task.

**3.3. Device components proposal:** this was a task simultaneously performed with the previous one although it lasted two more weeks. The aim of this task was to choose each component for the biosensors, from the communication method to the concrete layers of the ion-selective electrodes. Moreover, different alternatives were discussed and using different criteria, the one that would be ideal for the biosensor was chosen.

*Project memory*

**4.1. Writing the Final Degree Project memory**: this task lasted at least a month and a half if not a bit more and consisted on elaborating the memory of the pertinent final degree project where all the aspects aforementioned were thoroughly explained and discussed.

### 9.3. GANNT

Tasks and timings have also been represented using a GANTT chart in order to illustrate the schedule of the project. *Figure 10* shows the task flow of the project and the evolution and dependency of these tasks along the 6 months that this project took to be completed.

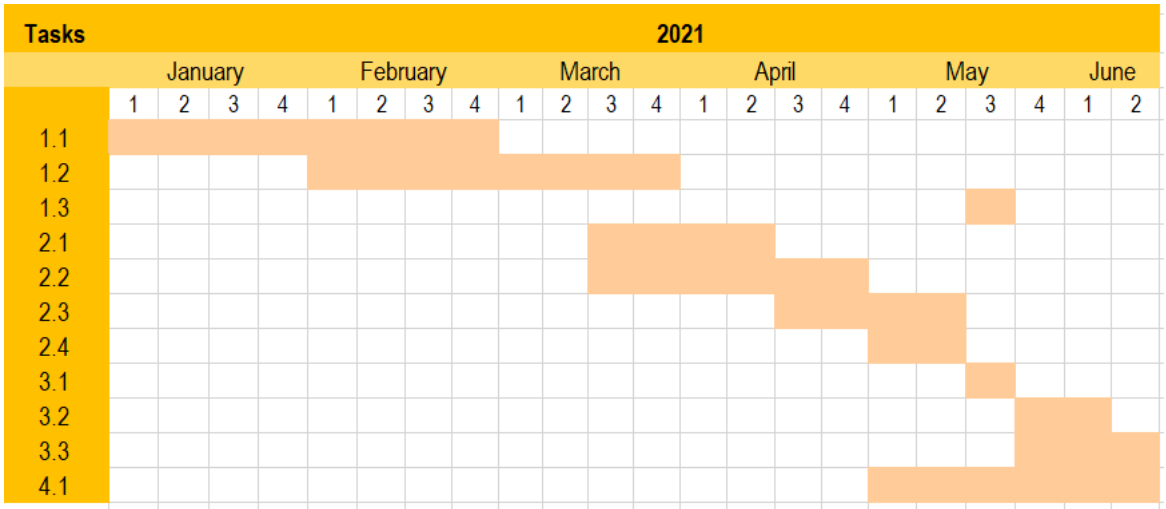


***Figure 10***. GANNT chart for this project.

# 10. Discussion and conclusions

Finally, as a summary, it has been extensively discussed the fulfilment of the initially planned objectives and also, new future perspective and opportunities of improvements that were discovered throughout the investigations performed in this project. Moreover, the challenges to overcome and the setbacks encountered.

## 10.1. Objectives fulfilment

As it was mentioned in previous sections, this work has always been considered as an initial step of investigation that aims to develop a device able to predict HE and that used many diagnostic tools to do so. It was never intended to complete the whole project presented, but to perform an initial step towards to development of the device.

Regarding the objectives that were set at the initial of the project that consisted on a thorough study on the symptoms and diagnostic tools for HE and the solutions available meant for other pathologies that could be applied in our project, we can determine that these stages were successfully completed.

However, another objective set was to perform a study of biomarkers where we aimed to find other ions that could have a correlation with HE. Although a thorough bibliographic research was performed, all the papers regarding the proposed ions, which were chosen because they can be found at large concentration in sweat, were based on hypothesis that have not yet been confirmed, therefore making the choosing of these ions very complicated and hypothetical.

Moreover, we had the same problem with the biosensor conceptualization stage. Since wearable sweat analytical devices are very new, which is proven by all the papers used in the conceptualization stage that were dated last year, most of them were never tested and were only conceptualized or were intended for other ions that did not include ammonium.

Therefore, although we can say that all the objectives set were performed and accomplished, there would be room for improvement regarding the study of biomarkers and the sensor conceptualization.

## 10.2. Future opportunities of improvement

In this section, some possible upgrades that could be implemented in the overall project and at the level of the biosensor will be discussed.

### *10.2.1. Project clinical improvements*

Regarding the overall project, it would be interesting to be able to integrate sweat sensors that can measure more than one analyte. Currently, most ion-detection sensors, as they are based on ISEs, can only measure one analyte or two at best.

Since there is a lack of information regarding the causes of the development of HE, multiple diagnostic tools must be included in the project to accurately predict the pathology. Currently, there are medical devices that can perform different diagnostic tasks, such as sensors that measure two different analytes or devices that measure both heart rate and temperature. Nonetheless, technology is not yet at the point where it allows us to integrate any kind of sensors.

Moreover, each medical device that has been studied in the market research section, needs to be located in a different part of the body. For instance, sweat sensors usually are placed at the back of the patient near the armpits, since perspiration is much present at that part of the body, and the devices that would detect hand "flapping", should be located on the wrists. This limits the integration of both devices.

Additionally, if we were to use many diagnostic tools on the patient without integrating them, we would limit the patient's mobility and would probably make him uncomfortable, even more considering that the device is supposed to be worn for life or until the liver condition is treated.

Therefore, we can conclude that there is a need for more trusted information regarding the cause of the pathology so we could narrow the use of diagnostic tools or just focus on the most important biomarkers, facilitating the integration of the devices and the patient's comfortability. This must, of course, go hand in hand with the pertinent improvements in the field of sensorics and medical technology in general.

### *10.2.2. Biosensor enhancements*

Regarding the sensor, there are many aspects of sweat sensing that must be further developed in order to take the field forward. Some challenges that these new devices pose, when being used in the medical sector for the first time, are associated with interpreting the sensor data results to perform a predictive diagnostic since they have not been interpreted before. Moreover, at the device level there is also the need to improve the packaging of the sensor into robust easy-to-wear systems that prevent the accumulation of noise produced by motion or strain. Also, reducing power consumption, would be another consideration for the advancement of sensors since it would allow an easy improvement of their service life.

Additionally, it is crucial to develop methods that induce sweat secretion in sedentary environments since it will allow the expansion of sweat-based sensors into the health monitoring field beyond sportive applications. Furthermore, the advancement of sweat sensor technology will enable non-invasive probing of our bodies at molecular levels benefiting diverse medical fields and enabling personalized and predictive healthcare.

### 10.3. Personal conclusions

As it was previously mentioned, the main purpose of this final degree project was to create a device that was able to predict HE. Although it was not possible to perform all the project that was originally proposed mainly due to lack of time and knowledge, an initial step towards the development of this project was performed.

I am content with the achievement of the objectives that were set and also to be a part of a project that intends to fulfil a real need that affects many people. It is worth mentioning that this project was started from zero, giving me the opportunity to learn various stages of project designing, not to mention, the opportunity to be part of a leading field of professional research at the Hospital Clínic.

By doing this project I have discovered my increasing interest for the sensorics field, which I had not yet studied. Being this one of the main areas of research in the biomedical engineering field, I do not discard focusing my career in biosensorics in the near future.

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